Using Joint Models to Estimate Causal Effects for Salvage Therapy after Prostatectomy

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Aims, Models & Estimands

1 Background & Aim

- Setting Patients treated with surgery after diagnosis of Prostate Cancer (PCa)
  - ▷ *remain at risk of metastasis*
- Follow-up
  - ▷ PSA levels at frequent intervals
  - ▷ when PSA increases, physicians consider Salvage Therapy (ST)
  - ▷ ST androgen deprivation therapy, radiation therapy, chemotherapy, and combinations

1 Background & Aim (cont'd)

- Important questions regarding Salvage Therapy
  - ▷ *who should take it?*
  - ▷ *when to start?*
  - ▷ *does it work?*

1 Background & Aim (cont'd)

Quantify the amount by which Salvage Therapy reduces the risk of metastasis

1 Background & Aim (cont'd)

- University of Michigan Prostatectomy Data
  - ▷ 3634 PCa patients followed-up in 1996–2013
    - * aged 40 to 84 years with clinically localized cT1 to cT3 disease
    - * received radical prostatectomy
  - ▷ baseline variables: PSA, Gleason, T-stage, age, race, gland volume, perineural invasion, planned adjuvant therapy

1 Background & Aim (cont'd)

- Challenges

  ▷ *Observational Data – no RCT*

  * selection bias
  * ascertainment bias

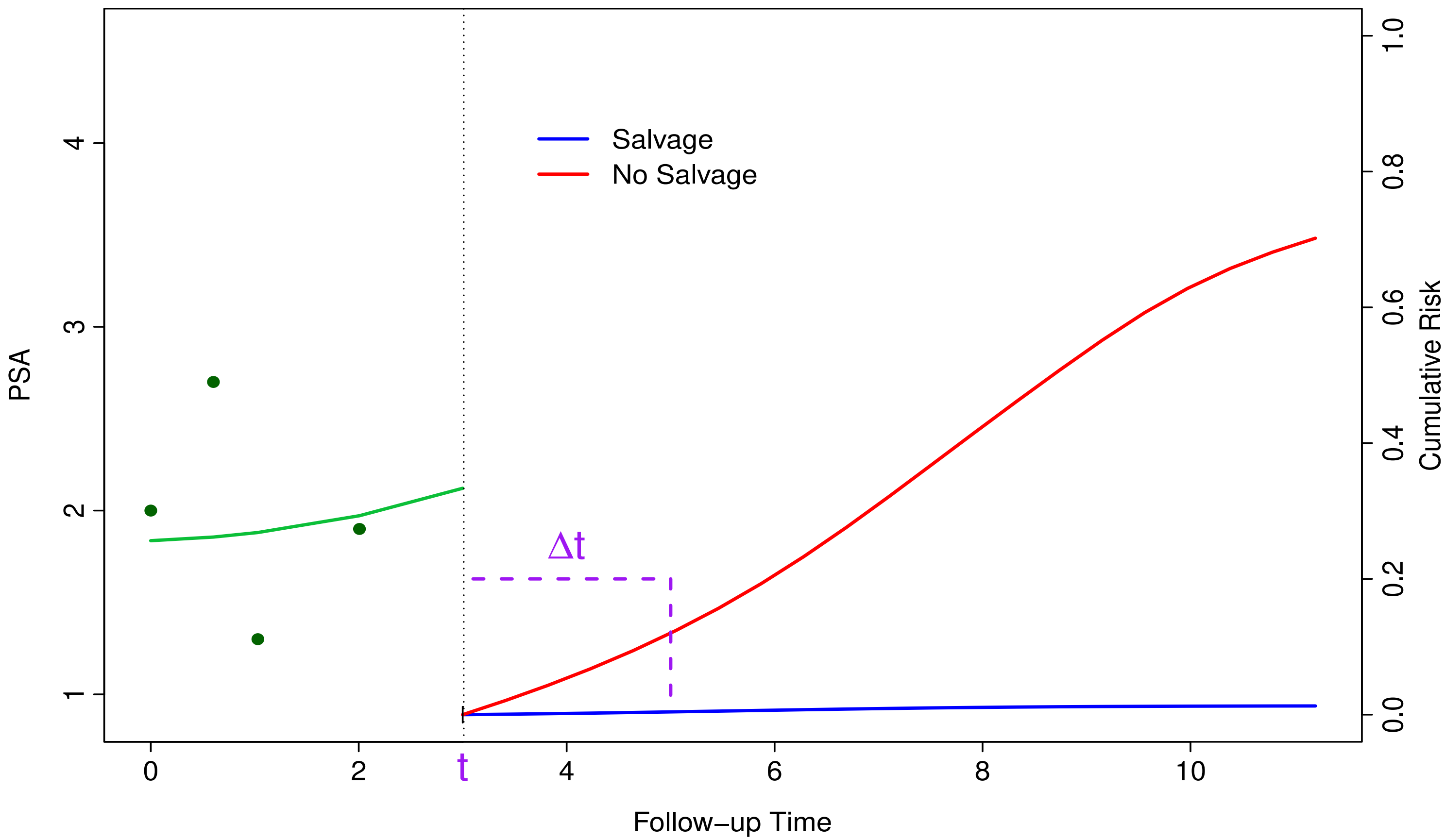
  ▷ *Time-Varying Salvage Therapy*

  * depends on previous PSA
  * PSA time-dependent confounder
  * endogeneity

2 Causal ST Effects

- Standard assumptions for Causal Inference
  - ▷ *Consistency:* Observed outcomes equal the counterfactual outcomes for the actually assigned treatment
  - ▷ *Sequential Exchangeability:* The counterfactual outcomes are independent of the assigned treatment conditionally on the history of PSA measurements and baseline covariates

2 Causal ST Effects (cont'd)



2 Causal ST Effects (cont'd)

Which is the target group?

- Notation
  - ▷ T_m: time to metastasis
  - ▷ T_d: time to death
  - ▷ $\mathcal{H}^*(t)$: a version of the PSA history up to t
  - ▷ $T_m^{(a)}$ and $T_d^{(a)}$ counterfactual outcomes
    - * $a = 1$, ST given at t
    - * $a = 0$, ST was not given in $[t, t + \Delta t]$

2 Causal ST Effects (cont'd)

- Marginal Salvage Therapy Effect

  ▷ we average over all PSA histories

$$\mathsf{ST}^M(t + \Delta t, t) =$$
$$\color{blue}{\Pr\{T_m^{(1)} \leq t + \Delta t \mid T_m > t, T_d > t\}} - \color{red}{\Pr\{T_m^{(0)} \leq t + \Delta t \mid T_m > t, T_d > t\}}$$

- Notes:

  ▷ of lesser relevance to the urologists because they decide who gets ST based on PSA $\Rightarrow$ **more bias**

  ▷ averages over a big group of patients $\Rightarrow$ **smaller variance**

2 Causal ST Effects (cont'd)

- Conditional Salvage Therapy Effect

  ▷ we condition on the PSA history of a specific patient, i.e., $\mathcal{H}^*(t) = \mathcal{H}_i(t)$

$$\begin{aligned}\mathsf{ST}^C(t + \Delta t, t) \;=\; & \Pr\{T_m^{(1)} \leq t + \Delta t \mid T_m > t, T_d > t, \mathcal{H}_i(t)\} \\ & - \Pr\{T_m^{(0)} \leq t + \Delta t \mid T_m > t, T_d > t, \mathcal{H}_i(t)\}\end{aligned}$$

- Notes:

  ▷ much more relevant to the urologists ⇒ **less bias**

  ▷ averages over a narrow group of patients ⇒ **larger variance**

2 Causal ST Effects (cont'd)

- Marginal-Conditional Salvage Therapy Effect

  ▷ consider ST for patients who had PSA levels above the threshold value c at their last visit, i.e., $\mathcal{H}^*(t) = \{Y(t) : Y(t) > c\}$

$$\text{ST}^{MC}(t + \Delta t, t) = \Pr\{T_m^{(1)} \leq t + \Delta t \mid T_m > t, T_d > t, \mathcal{H}^*(t)\}$$

$$- \Pr\{T_m^{(0)} \leq t + \Delta t \mid T_m > t, T_d > t, \mathcal{H}^*(t)\}$$

- Notes:

  ▷ relevant to the urologists ⇒ **compromised bias**

  ▷ averages over a bigger group of patients ⇒ **compromised variance**

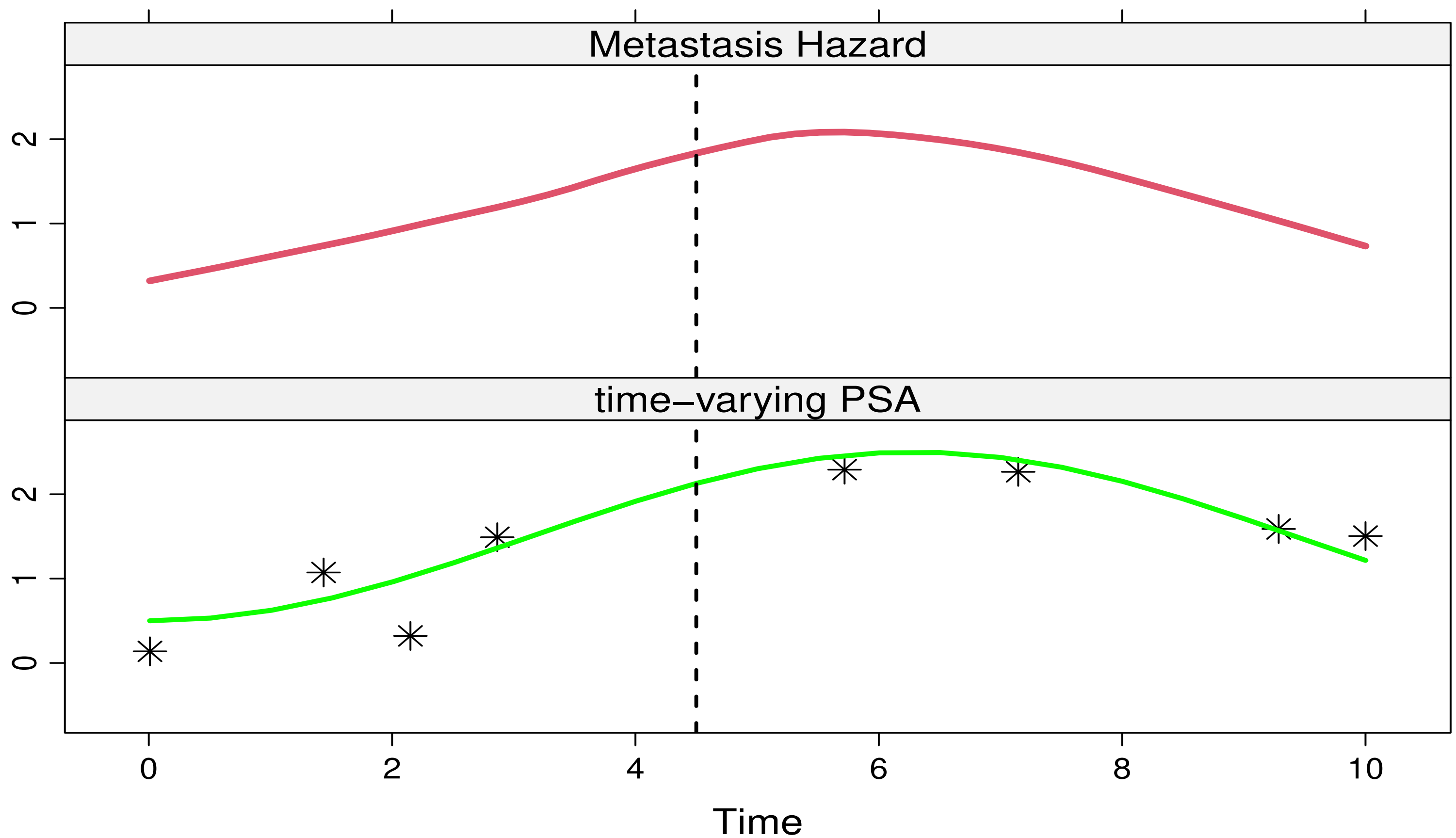
3 Structural Models

Standard Cox models not appropriate

$\Downarrow$

Joint Models for Longitudinal and Time-to-Event Data

3 Structural Models (cont'd)



3 Structural Models (cont'd)

Joint models completely specify the joint distribution of PSA, time-to-metastasis & time-to-death

- Under sequential ignorability,
  - ▷ they provide valid marginal distributions
  - ▷ *without requiring* to model the treatment assignment mechanism

4 PSA Sub-Model

- As PSA increases, patients may receive ST

- We let S_i denote the time a patient initiated ST
  - ▷ for patients who did not initiate ST, $S_i = \infty$

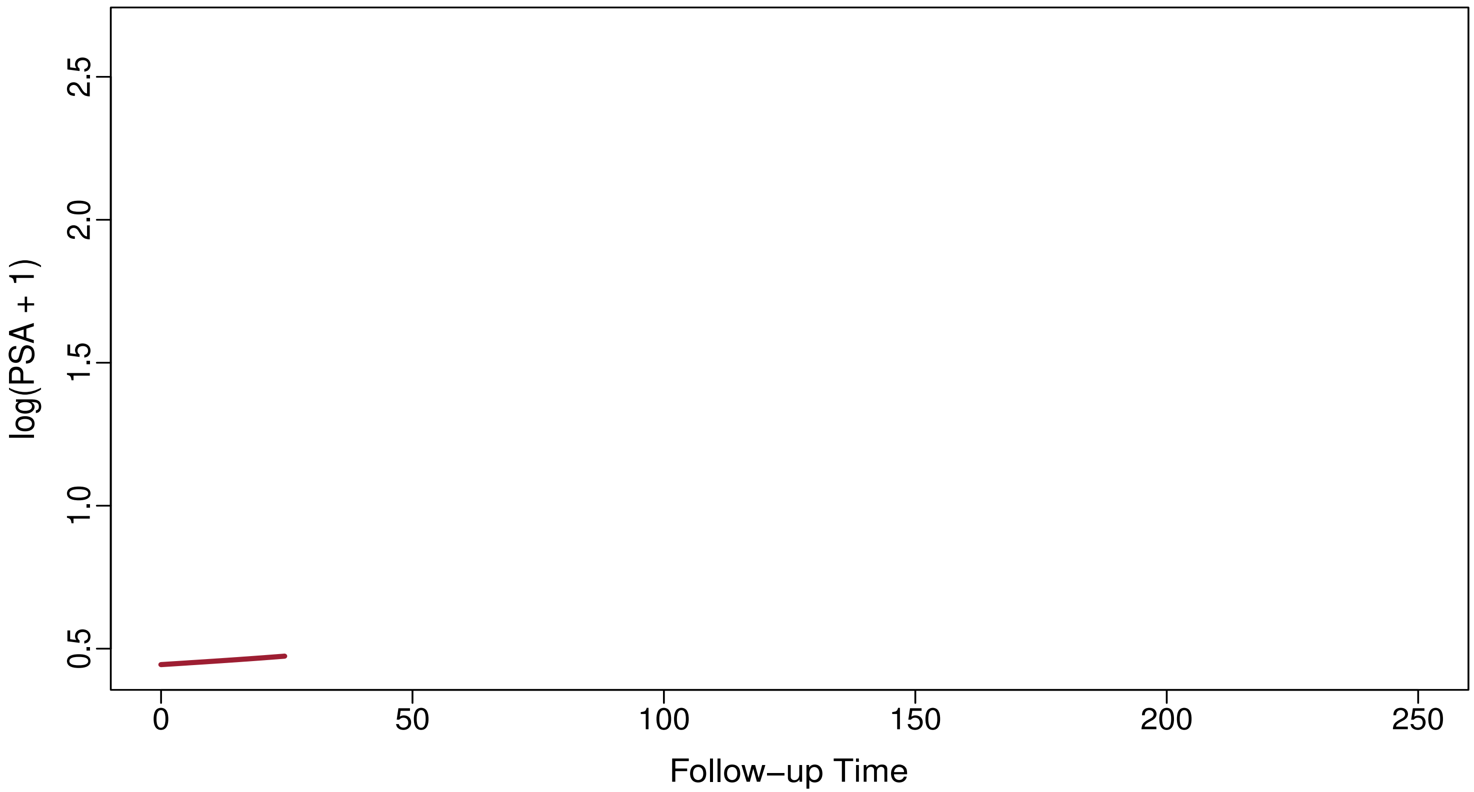
- After ST, PSA levels are expected to drop
  - ▷ but may rise again before metastasis

4 PSA Sub-Model (cont'd)

$$\log\{\mathsf{PSA}_i(t) + 1\} = \begin{cases} \eta_i(t) + \varepsilon_i(t) = \boldsymbol{x}_i(t)\boldsymbol{\beta} + \boldsymbol{z}_i(t)\boldsymbol{b}_i + \varepsilon_i(t), \ \ t < S_i \\ \\ \tilde{\eta}_i(t) + \varepsilon_i(t) = \\ \quad \eta_i(t) + \Big\{\tilde{\boldsymbol{x}}_i(\tilde{t})\tilde{\boldsymbol{\beta}} + \tilde{\boldsymbol{z}}_i(t)\tilde{\boldsymbol{b}}_i\Big\} + \varepsilon_i(t), \quad t \geq S_i, \end{cases}$$

$$\boldsymbol{u}_i = (\boldsymbol{b}_i, \tilde{\boldsymbol{b}}_i) \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Omega})$$

4 PSA Sub-Model (cont'd)



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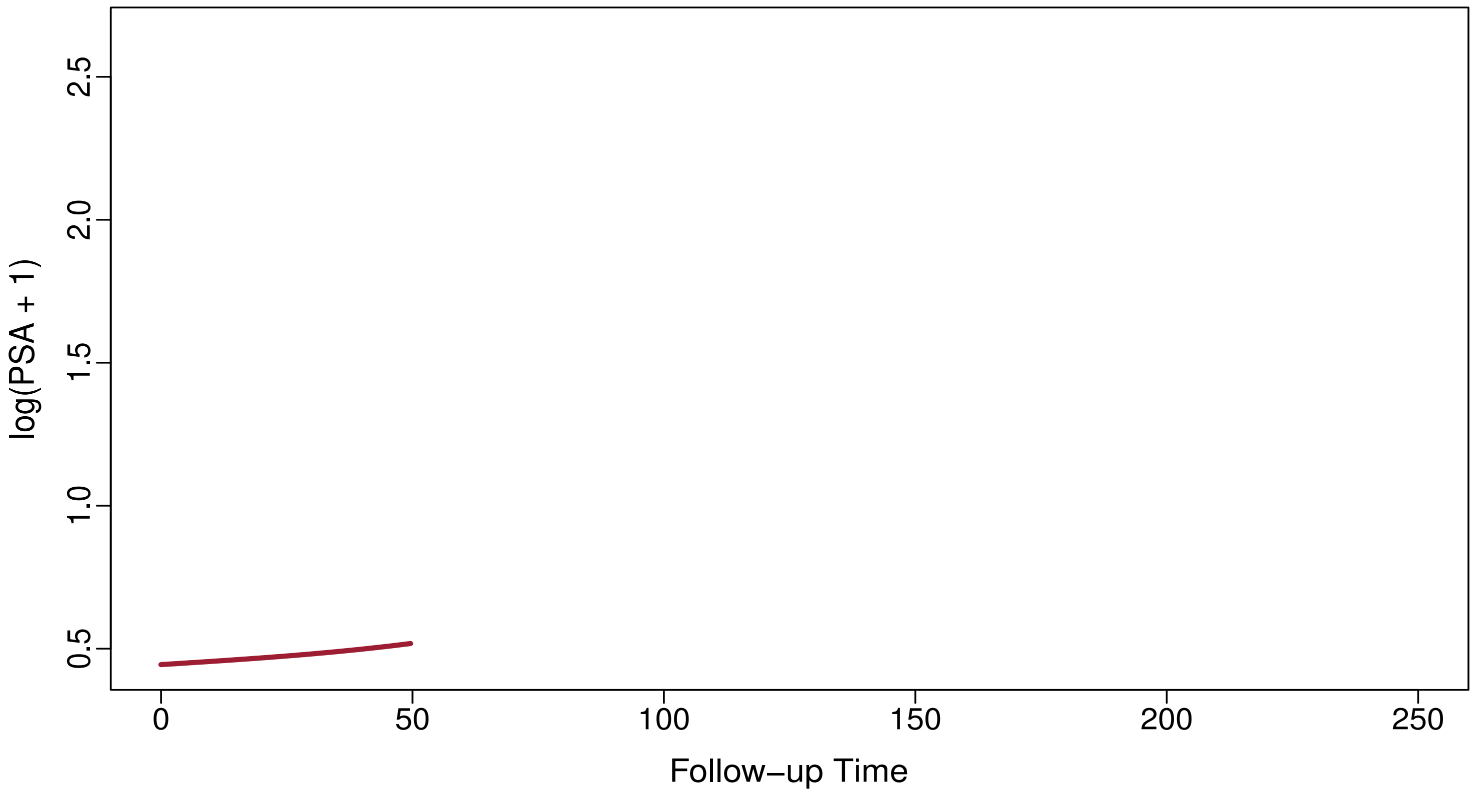

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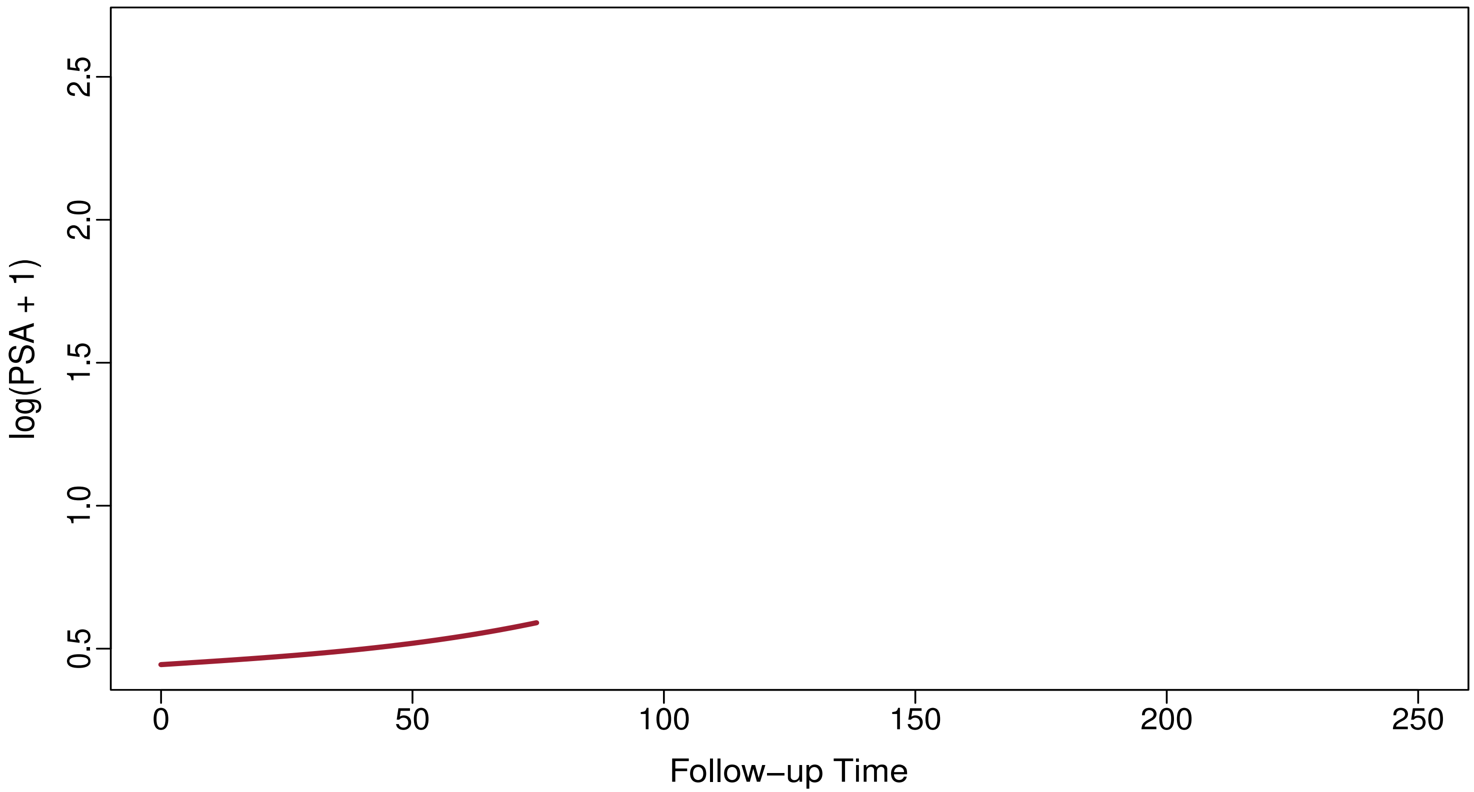
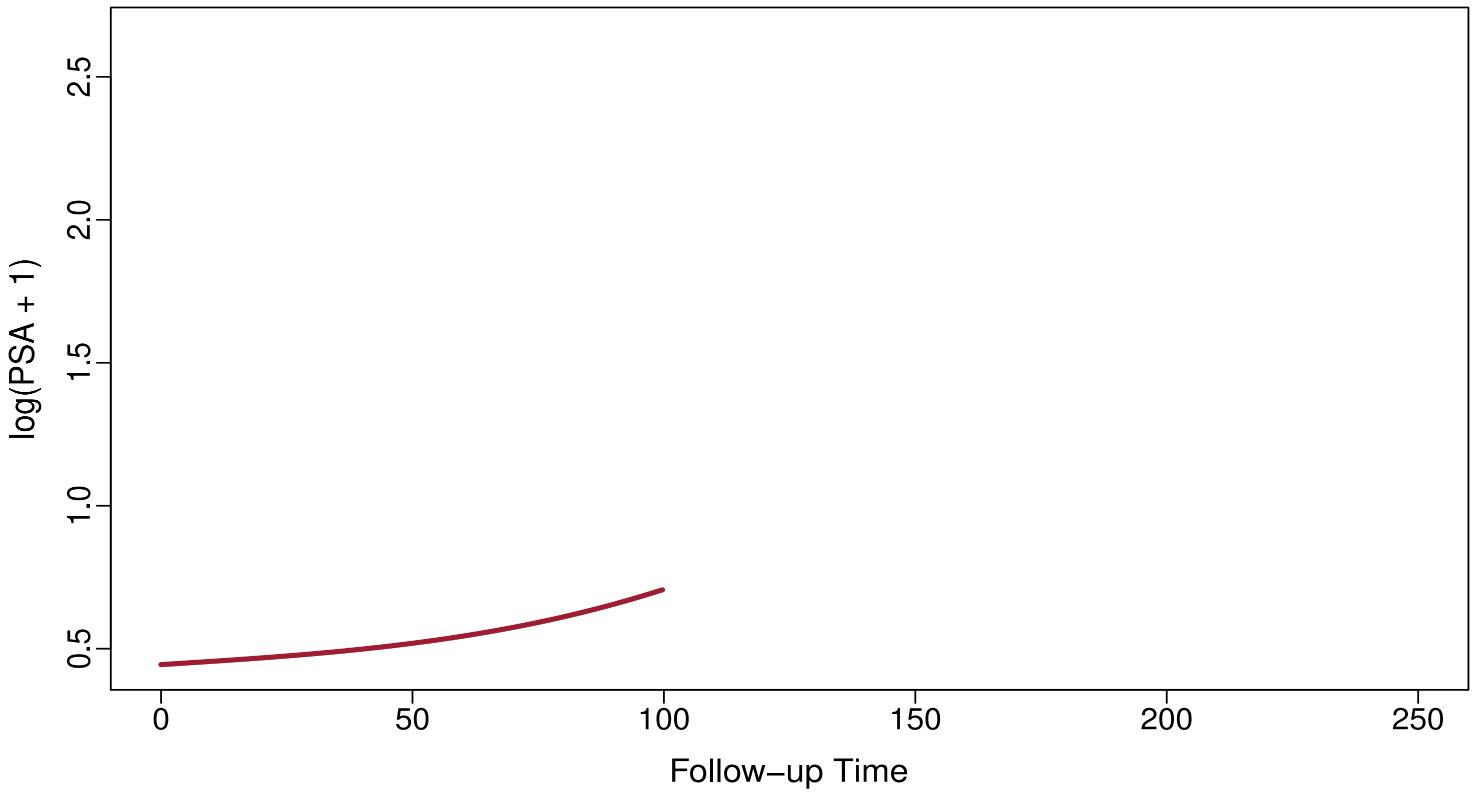
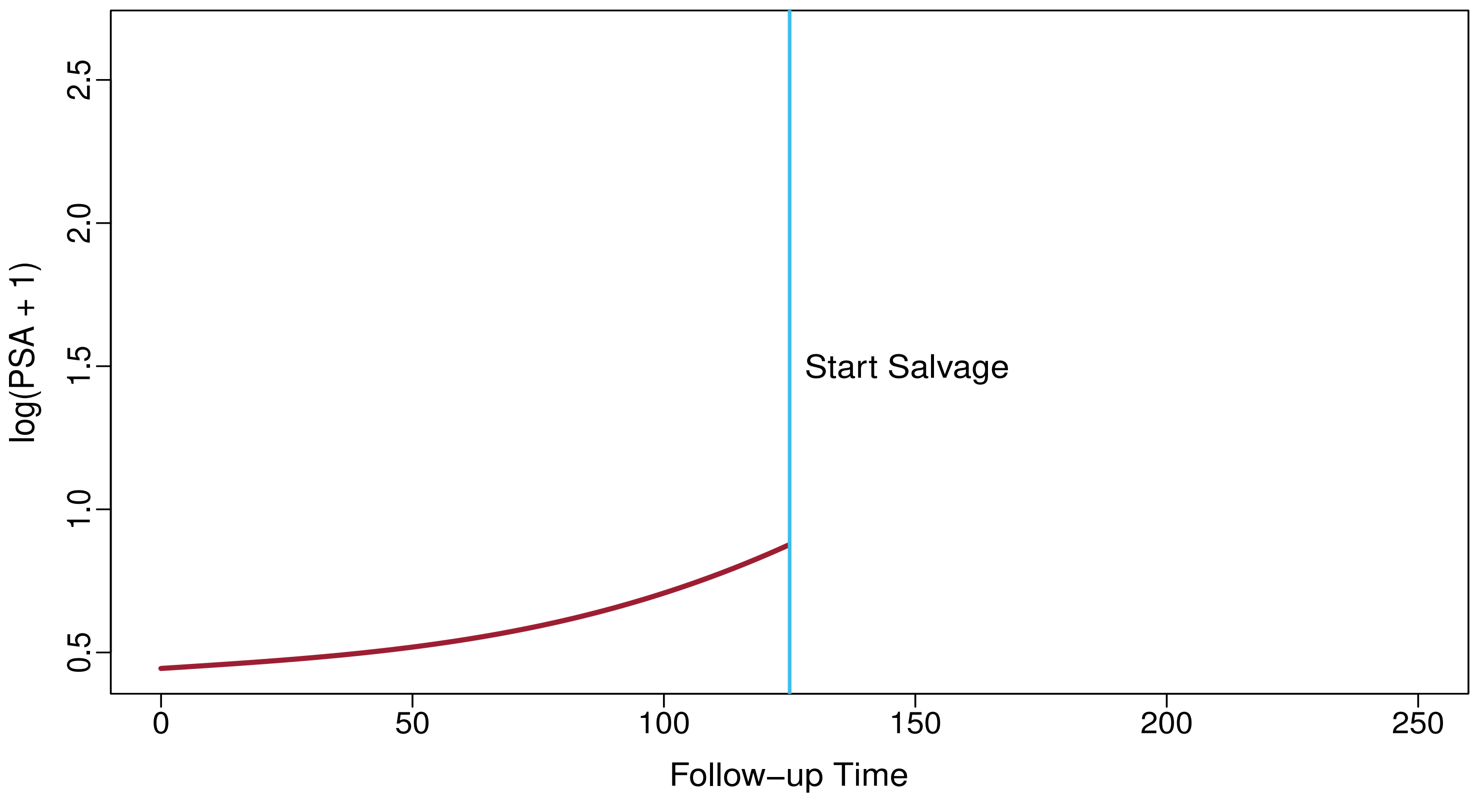


4 PSA Sub-Model (cont'd)



4 PSA Sub-Model (cont'd)



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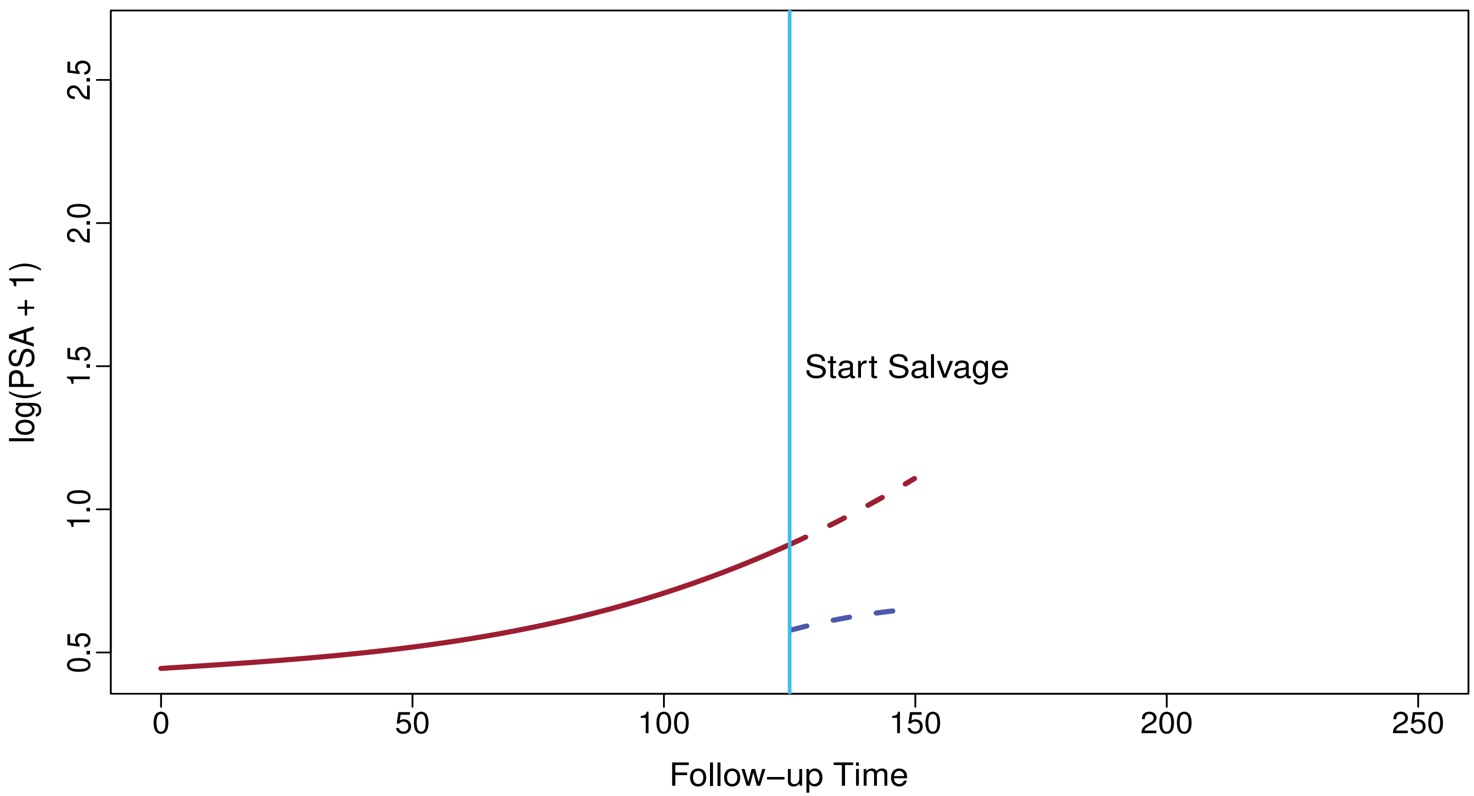

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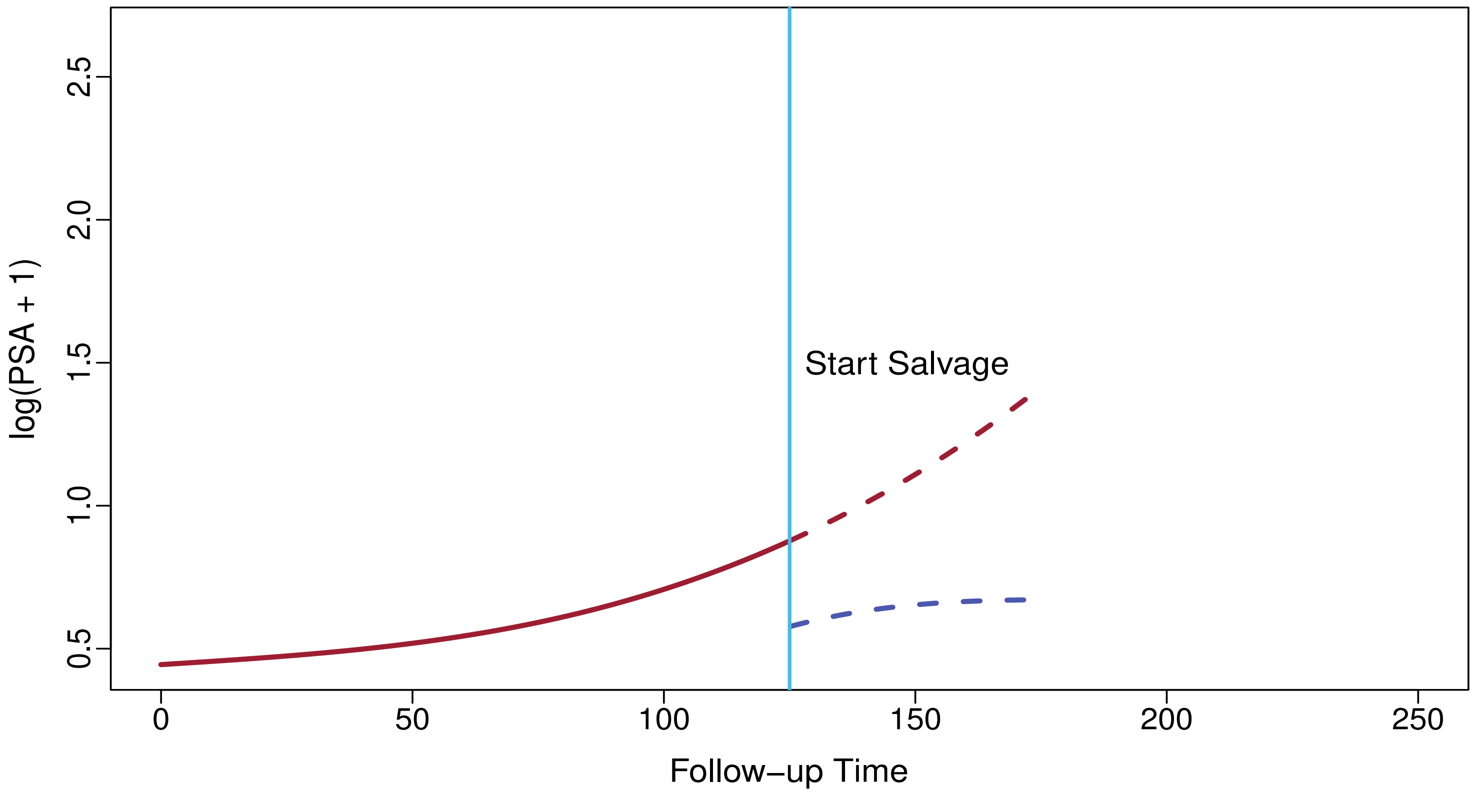

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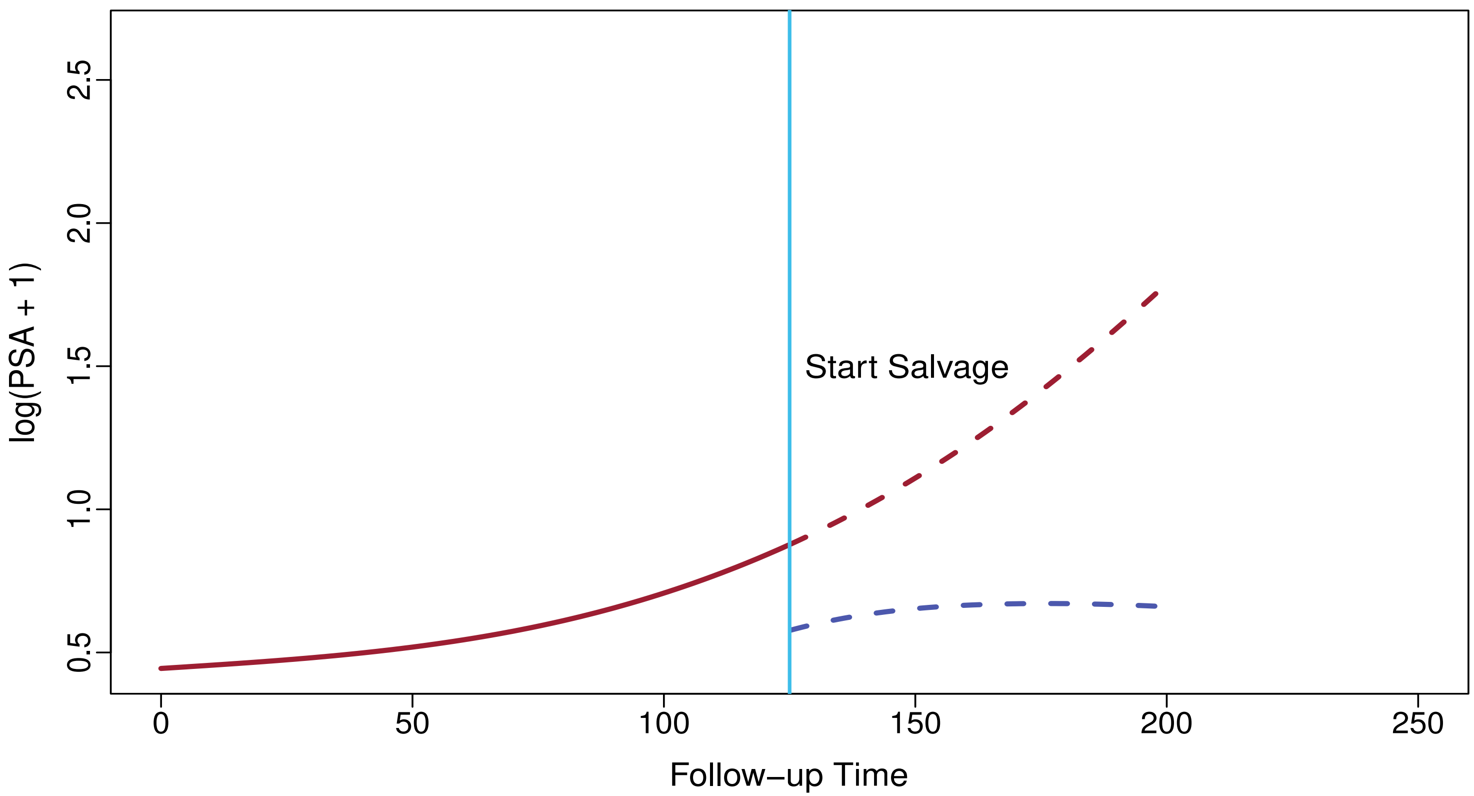
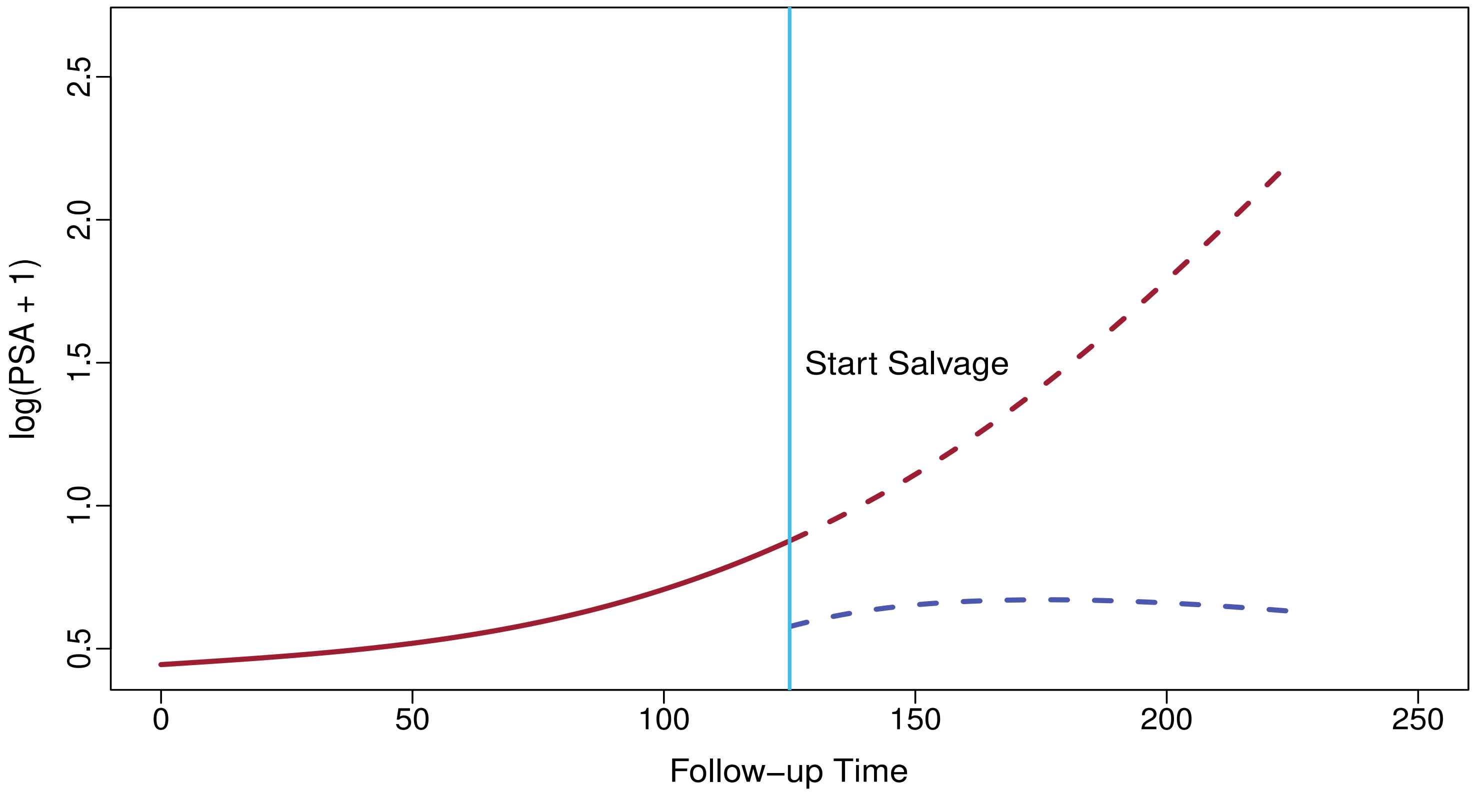
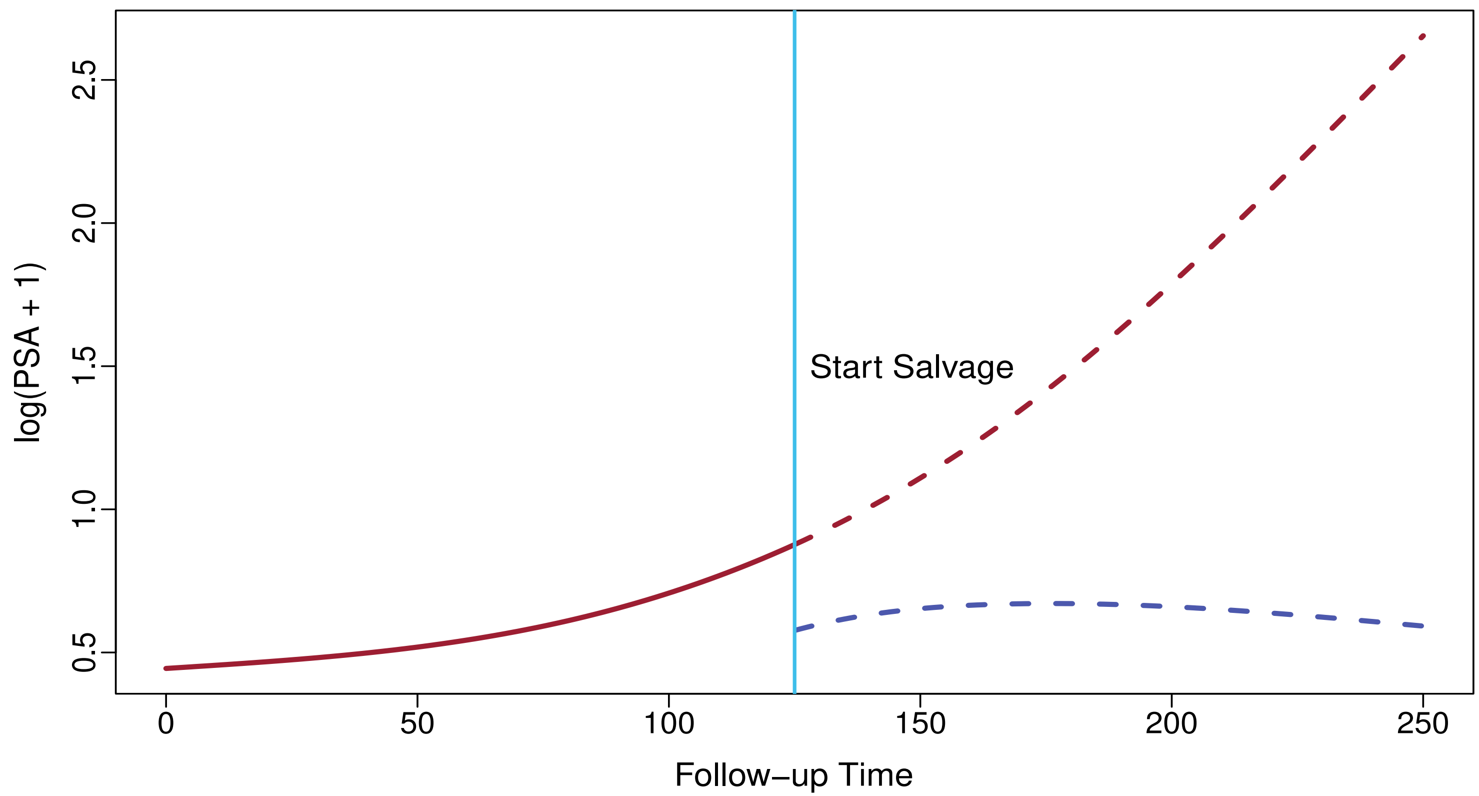


4 PSA Sub-Model (cont'd)



4 PSA Sub-Model (cont'd)



5 Metastasis and Death Sub-Models

- Metastasis and Death treated as *Competing Risks*

- Separate hazard models for metastasis and death
  - ▷ linked with PSA and ST
  - ▷ baseline covariates

5 Metastasis and Death Sub-Models (cont'd)

- Metastasis Sub-Model linked to baseline covariates, Salvage and PSA

$$h_i^m(t) = \begin{cases} h_0^m(t) \exp\Big(\boldsymbol{\psi}_m^\top \boldsymbol{w}_i + {\boldsymbol{\alpha}_m}^\top f\{\eta_i(t)\}\Big), & t < S_i \\ \\ h_0^m(t) \exp\Big(\boldsymbol{\psi}_m^\top \boldsymbol{w}_i + \gamma_m(t - S_i) + {\boldsymbol{\xi}_m}^\top g\{\tilde{\eta}_i(t)\}\Big), & t \geq S_i \end{cases}$$

5 Metastasis and Death (cont'd)

- Death Sub-Model linked to baseline covariates, Salvage *but not* PSA

$$h_i^d(t) = \begin{cases} h_0^d(t) \exp(\boldsymbol{\psi}_d^\top \boldsymbol{w}_i), & t < S_i \\ \\ h_0^d(t) \exp(\boldsymbol{\psi}_d^\top \boldsymbol{w}_i + \gamma_d), & t \geq S_i \end{cases}$$

6 Causal Effect Estimation

- From the joint model, we can obtain the conditional causal effect

$$\Pr\{T_{mi}^{(a)} \leq t + \Delta t \mid T_{mi} > t, T_{di} > t, \mathcal{H}_i(t), \mathcal{X}_i\} =$$

$$\int \int \Pr\{T_{mi}^{(a)} \leq t + \Delta t \mid T_{mi} > t, T_{di} > t, \boldsymbol{u}_i, \mathcal{X}_i, \boldsymbol{\theta}\}$$

$$\times \, p\{\boldsymbol{u}_i \mid T_{mi} > t, T_{di} > t, \mathcal{H}_i(t), \mathcal{X}_i, \boldsymbol{\theta}\} \, p(\boldsymbol{\theta} \mid \mathcal{D}) \, \mathrm{d}\boldsymbol{u}_i \mathrm{d}\boldsymbol{\theta}$$

  - ▷ $a = \{0, 1\}$
  - ▷ $\mathcal{D} = \{T_i, \delta_i, Y_i; i = 1, \ldots, n\}$
  - ▷ $p(\boldsymbol{\theta} \mid \mathcal{D})$ posterior

6 Causal Effect Estimation (cont'd)

- Monte Carlo scheme to estimate $\mathsf{ST}_i^C(t + \Delta t, t)$
  - ▷ sample $\breve{\boldsymbol{\theta}}^{(l)}$ from the posterior of the parameters $[\boldsymbol{\theta} \mid \mathcal{D}]$
  - ▷ sample $\breve{\boldsymbol{u}}_i^{(l)}$ from the posterior of the random effects $[\boldsymbol{u}_i \mid T_{mi} > t, T_{di} > t, \mathcal{H}_i(t), \mathcal{X}_i, \breve{\boldsymbol{\theta}}^{(l)}]$
  - ▷ calculate $\pi_i^{(l)}(t + \Delta t \mid t, a) = \Pr\{T_{mi}^{(a)} \leq t + \Delta t \mid T_{mi} > t, T_{di} > t, \breve{\boldsymbol{u}}_i^{(l)}, \mathcal{X}_i, \breve{\boldsymbol{\theta}}^{(l)}\}$

- We repeat L times and get

$$\widehat{\mathsf{ST}}_i^C(t + \Delta t, t) = \frac{1}{L} \sum_{l=1}^{L} \pi_i^{(l)}(t + \Delta t \mid t, a = 1) - \pi_i^{(l)}(t + \Delta t \mid t, a = 0)$$

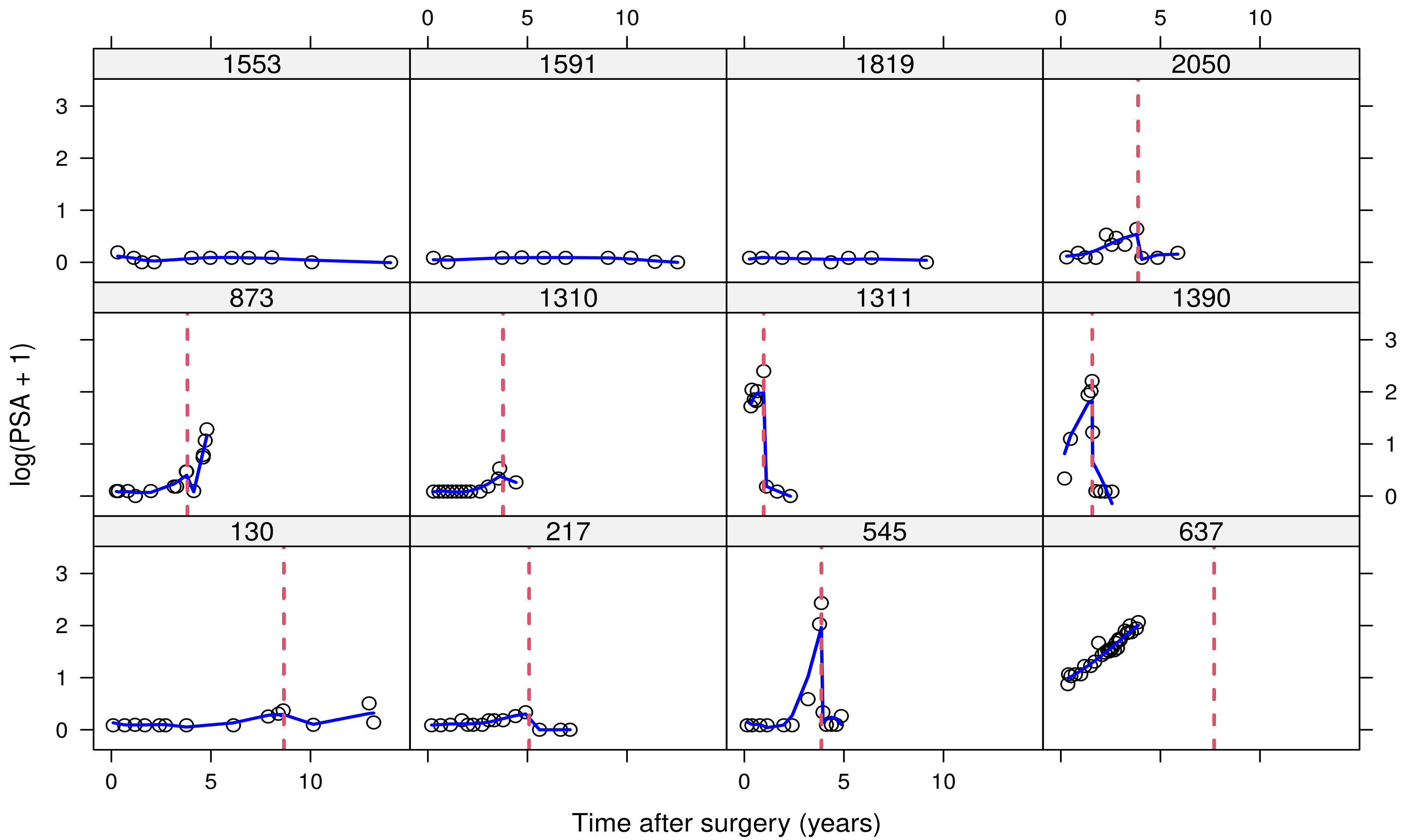
6 Causal Effect Estimation (cont'd)

- Estimation of $\mathsf{ST}^M(t+\Delta t, t)$ and $\mathsf{ST}^{MC}(t+\Delta t, t)$ proceeds by averaging the conditional effects over the respective groups of patients

- For example, for $\mathsf{ST}^M(t+\Delta t, t)$
  - ▷ $\mathcal{R}(t)$ the subset of patients at risk at time t
  - ▷ for each patient in $\mathcal{R}(t)$, we calculate $\widehat{\mathsf{ST}}_i^C(t+\Delta t, t)$

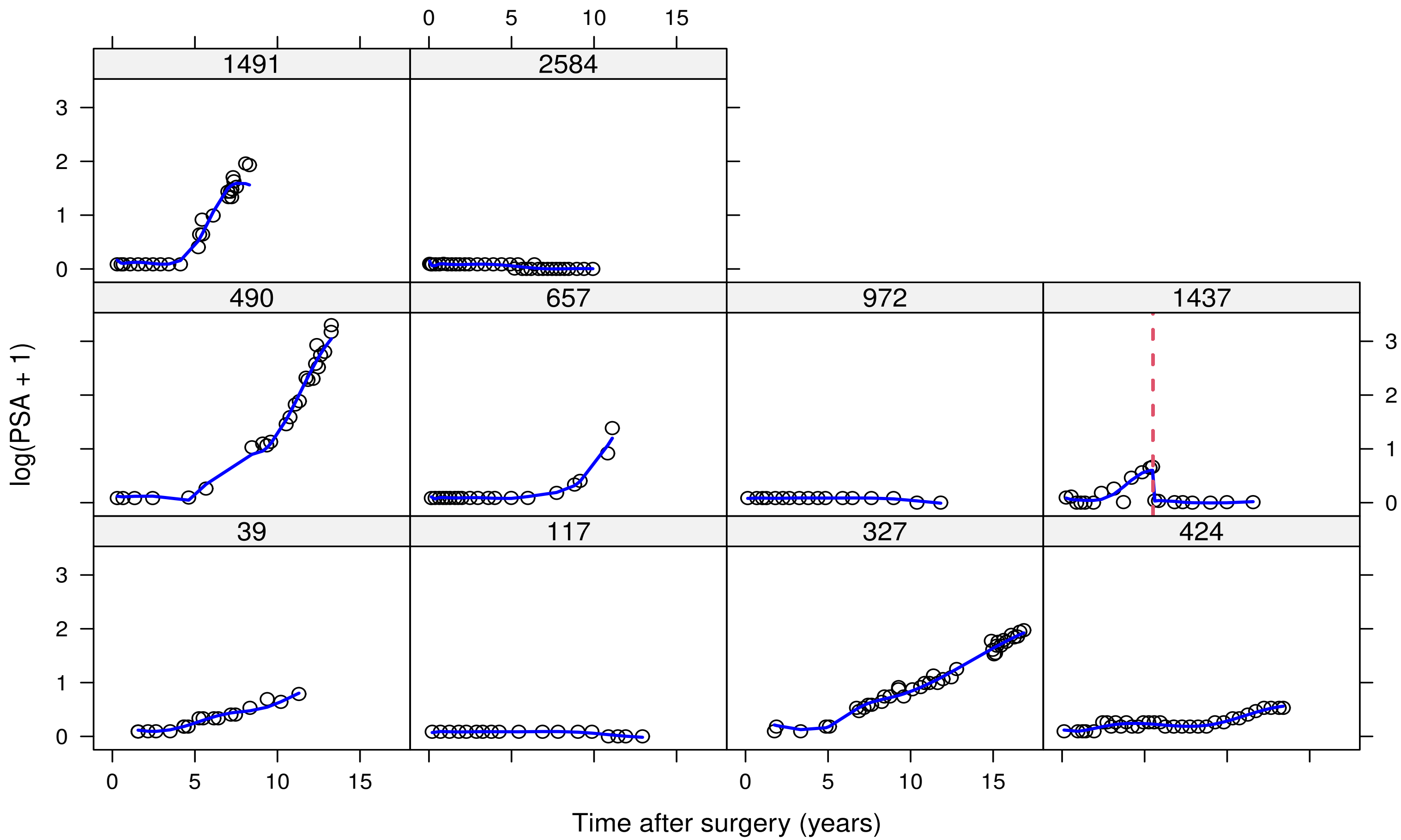
$$\widehat{\mathsf{ST}}^M(t+\Delta t, t) = n_r^{-1} \sum_{i:i\in R(t)} \widehat{\mathsf{ST}}_i^C(t+\Delta t, t),$$

7 Results

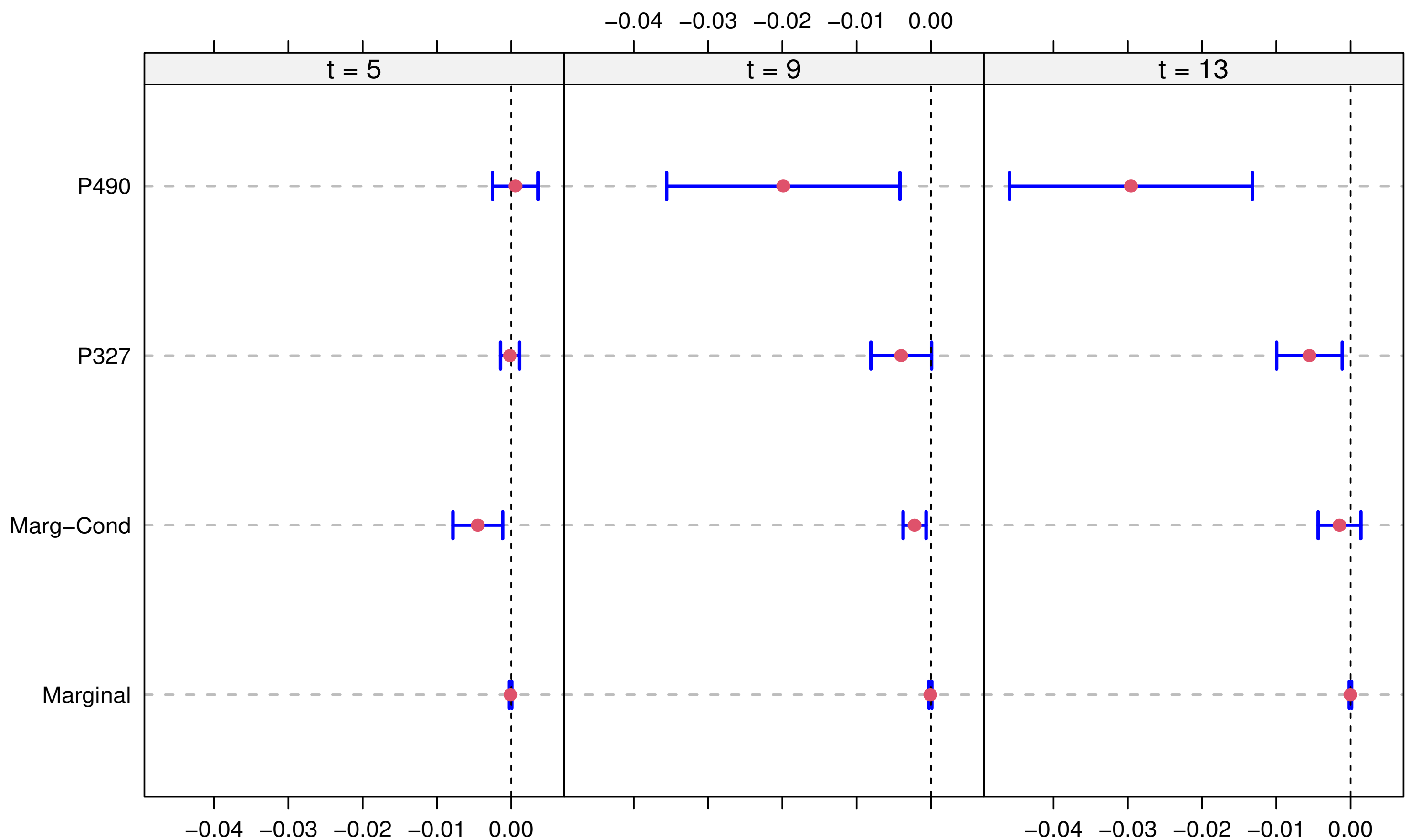


1553
1591
1819
2050
873
1310
1311
1390
130
217
545
637
0
5
10
0
1
2
3
log(PSA + 1)
Time after surgery (years)

7 Results (cont'd)



7 Results (cont'd)



7 Software (cont'd)

- Implementation available in **JMbayes2**
  - ▷ `predict()` cumulative incidence risks
  - ▷ `causal_effects()` calculates the different causal effects (not yet in the package, but in GitHub)

- Shiny app...

Thank for your attention!

https://www.drizopoulos.com/